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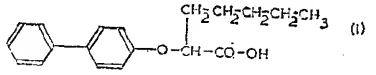
(54) NEW ARYLOXYALKANOIC ACID AND SALTS THEREOF

(71) We, J. R. GEIGY A.G., a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns processes for the production of a new aryloxyalkanoic acid and salts thereof having valuable pharmacological properties, these compounds as new substances, pharmaceutical preparation containing these compounds and the use thereof.

The 2 - (4 - biphenylyloxy) - heptanoic acid of formula I



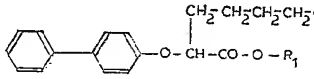
(I)

and salts thereof with inorganic and organic bases have not been described hitherto. It has now been found that these acids and their salts possess valuable pharmacological properties. In particular, they exhibit hypolipemic activity in a broad sense, which can be shown for example by the lowering the cholesterine and triglyceride level in the blood and liver on repeated oral administration to male rats.

The extraction of the serum and liver lipides is carried out according to Folch at al., J. Biol. Chem. 226, 497 (1957). The triglycerides are determined according to Kessler and Lederer, Technicon Symposia, vol. I (1965) and the cholesterol is determined according to Block et al., Technicon Symposia vol. I (1965) with the autoanalyzer.

The 2 - (4 - biphenylyloxy)-heptanoic acid and salts thereof are further characterised by a long persistence in the plasma and low toxicity. They are suitable for oral and rectal administration to mammals for the treatment of hyperlipemic conditions, such as for example hypercholesterinemia.

The 2 - (4 - biphenylyloxy) - heptanoic acid are and its pharmaceutically acceptable salts are produced in a first process by hydrolysing esters thereof of the general formula II



(II)

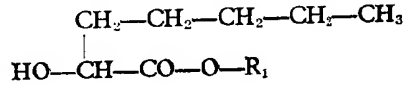
wherein

R_1 denotes a hydrocarbon radical, in particular a low alkyl radical having at most 6 carbon atoms or the cyclohexyl-, phenyl- or benzyl radical, and when required, converting a salt of 2 - (4 - biphenylyloxy) - hep - tanoic acid thus obtained into the free acid or converting the free acid or a salt thereof thus obtained into, or into another, pharmaceutically acceptable salt thereof.

In a further process, 2 - (4 - biphenylyl - oxy) - heptanoic acid and its pharmaceutically acceptable salts are produced by hydrolysing the corresponding nitrile, amide or imido alkyl ester thereof, the imido alkyl ester moiety having at most 6 carbon atoms; the free acid or a pharmaceutically acceptable salt thereof being obtained as described above if desired. Hydrolysis is carried out for example by heating in an alkanolic or aqueous - alkanolic alkali - hydroxide solution. From the alkali salt solutions of the 2 - (4 - biphenylyloxy) - heptanoic acid thus obtained, the corresponding pure alkali salt can be prepared either directly by concentrat-

ing or evaporating and recrystallising, or by firstly liberating the acid and then, purifying, e.g. by recrystallisation, and reconverting into a salt with a suitable inorganic or organic base. The above stated derivatives of 2 - (4 - biphenylyloxy) - heptanoic acid can moreover also be converted in an acid medium, e.g. by heating in a solution of a 60—70% sulphuric acid or in alkanolic - aqueous hydrochloric acid, into the free acid.

The esters of the general formula II, and also the corresponding nitriles, amides and low imidoalkyl esters, are new compounds. To produce esters of general formula II, an alkali metal salt of p - phenylphenol is reacted with one of the below defined esters which are reactive with respect to the 2 - hydroxy group of a 2 - hydroxy heptanoic acid ester of general formula III



(III)

wherein R_1 has the meaning given under formula II, in a suitable solvent, such as ethanol at its boiling temperature or in dimethyl formamide at 40—130°, preferably at 60—90°. The required alkali metal salt of p - phenylphenol can be used as such, or can be produced prior to the reaction in situ, in ethanol for example by means of the corresponding alkali metal ethylate, or in dimethyl formamide using a suitable alkali metal hydride, in particular sodium- or lithium hydride.

The esters reactive with respect to the 2 - hydroxy group of compounds of general formula III are the halogenides, e.g. esters of 2 - halogen heptanoic acids, and derivatives of arsenesulphonic acids and alkane sulphonic acids, e.g. 2 - (4 - toluene - sulphonyloxy)- and 2 - methane sulphonyloxy heptanoic acid esters. Some of these compounds, e.g. 2 - bromoheptanoic acid ethyl ester, are known, others can be obtained, analogously to the known compounds and/or corresponding derivatives, from lower alkanoic acids containing at most 6 carbon atoms. Analogously to the reactive esters of compounds of the general formula III, reactive esters of 2 - hydroxy heptanoic acid nitrile, e.g. the known 2 - bromoheptanoic acid nitrile, can also be reacted with alkali metal salts of p - phenylphenol. The obtained nitrile of the 2 - (4 - biphenylyloxy) - heptanoic acid is either hydrolysed directly to form the acid, or if desired converted in a manner as known per se into the corresponding amide or into a low imidoalkyl ester, having at most 6 carbon atoms in the imidoalkyl ester moiety, or the hydrohalogenide thereof, i.e. into further starting substances suitable for hydrolysis to obtain 2 - (4 - biphenylyloxy) heptanoic acid or salts thereof.

Furthermore, the nitrile and the amide of 2 - (4 - biphenylyloxy) - heptanoic acid can also be produced starting from lower alkyl esters of 2 - (4 - biphenylyloxy) - n - pentyl-cyano - acetic acid having at most 6 carbon atoms in the alkyl moiety, the production of which is given further below. Thus by partial hydrolysis of a substituted cyanoacetic acid alkyl ester as aforesaid with an approximately equimolar amount of an aqueous or alkanolic alkali metal hydroxide solution, followed by acidification and then decarboxylation, the desired nitrile is obtained. By boiling a substituted alkyl ester of cyano - acetic acid as aforesaid with an excess of alkanolic alkali hydroxide solution and then acidifying, the monoamide of the substituted malonic acid is obtained, possibly mixed with the free, substituted acid and the desired ultimate end product, the 2 - (4 - diphenylyloxy) - hep - tanoic acid of formula I. By decarboxylating, the amide of 2 - (4 - biphenylyloxy) - hep - tanoic acid or a mixture of the aforesaid with the free acid is obtained, which free acid can be converted exactly as the pure amide into the same final product.

According to a further process, 2 - (4 - biphenylyloxy) - heptanoic acid and its salts can be obtained by heating a di - lower alkyl ester or a lower alkyl - nitrile ester, each alkyl residue having at most 6 carbon atoms, or the dinitrile of (4 - biphenylyloxy) - n - pentyl - malonic acid, with an inorganic or organic base until an equimolar amount of carbon dioxide is split off and, when required, converting the salt of the 2 - (4 - biphenylyloxy) - heptanoic acid thus obtained into the free acid or into another pharmaceutically acceptable salt with an inorganic or organic base. For example, the dialkyl ester of (4 - biphenylyloxy) - n - pentyl - malonic acid is refluxed with excess alkanoic alkali hydroxide solution, e.g. with methanolic potassium hydroxide solution, for several hours. The conversion of the alkyl - nitrile ester and the dinitrile are analogous, but the conditions are more strenuous, e.g. longer reaction times and/or higher temperatures in a closed container.

The di- lower alkyl esters, the alkyl - nitrile esters and the dinitrile of (4 - bi - phenylyloxy) - n - pentyl - malonic acid, as well as the acid itself, are new compounds. They can be produced, for example analogously to the esters of the general Formula III by reacting a dialkyl ester of bromo- or chloro - n - pentyl - malonic acid or an alkyl ester of bromo- or chloro - n - pentyl - cyano - acetic acid or of bromo - n - pentyl - malonitrile with an alkali metal salt of p - phenyl - phenol, e.g. in boiling abs. ethanol. The bromo- and chloro - compounds needed as starting materials are obtained, for

example, by halogenating in an analogous manner to corresponding, known compounds having an alkyl group, e.g. diethyl bromo - n - butyl malonate [J. Am. Chem. Soc. 44, 1578—1581 (1922)].

According to yet a further process, 2 - (4 - biphenylyloxy) - heptanoic acid and salts thereof are obtained by heating (4 - bi - phenylyloxy) - n - pentyl malonic acid or a salt thereof with an inorganic or organic base, in particular a monoalkali metal salt thereof, until the equimolar amount of carbon dioxide is split off, and converting the acid obtained using the free dicarboxylic acid if desired into a salt with an inorganic or organic base. The stated dicarboxylic acid is for example heated to temperatures between 130—200°, until the evolution of carbon dioxide has finished. The 2 - (4 - biphenylyl - oxy) - malonic acid is, for example, obtained by hydrolysis of its corresponding low dialkyl esters or of corresponding nitrile - alkyl esters, i.e. (4 - biphenylyloxy) - n - pentyl malonic acid dialkyl esters or (4 - biphenylyloxy) - n - pentyl cyanoacetic acid alkyl esters with alkanolic or aqueous - alkanolic potassium hydroxide solution or sodium hydroxide solution at slightly elevated temperature and subsequent acidification. According to one form of the process according to the invention, one of the already mentioned malonic acid low dialkyl esters, nitrile - alkyl esters or the dinitrile, is heated with a hydrous mineral acid, whereby the dicarboxylic acid occurring as a result of hydrolysis, is decarboxylated under the reaction conditions directly to form 2 - (4 - biphenylyloxy) - heptanoic acid. As hydrous mineral acid can be used for example 60—70% sulphuric acid or in a closed vessel concentrated hydrochloric acid, to which can be added an organic solvent of suitable boiling-point for example acetic acid, which is water-soluble or which can be mixed with water.

A further process for producing 2 - (4 - biphenylyloxy) - heptanoic acid and salts thereof comprises reacting an alkali metal salt of p - phenylphenol with a salt of an ester reactive with respect to the 2 - hydroxy group of 2 - hydroxy heptanoic acid, liberating if desired the acid from the obtained salt and/or if desired converting the acid into a pharmaceutically acceptable salt, or by double reaction, the initially obtained salt directly into another salt, which is pharmaceutically acceptable, with an inorganic or organic base. The reaction is performed preferably in a solvent or diluent, e.g. in an optionally hydrous alkanol, such as ethanol or butanol, or in dimethyl formamide at a temperature of about 80° up to the boiling temperature of the reaction medium. Formation of the salts required as direct reaction constituents, from the free p - phenylphenol or from the free acid, occurs preferably in situ, for example as a result of adding an alkali metal alcoholate, an alkali hydroxide or alkali metal hydride, depending on whether a hydrous alkanol, an anhydrous alkanol or dimethyl formamide be used as the reaction medium. The reactive esters of the 2 - hydroxy heptanoic acid are the hydrohalic- arenesulphonic- and alkanesulphonic acid esters, known examples being 2 - bromoheptanoic acid and 2 - chloro - heptanoic acid.

If desired, the salts of 2 - (4 - biphenylyloxy) - heptanoic acid to be produced as pharmaceutically active substances are in general those, the cation of which exhibits, with regard to the dosages in question, no biologically inherent effect, or else a desired inherent effect, and the solubility of which in the stomach and intestinal contents ensures adequate adsorption. Salts which do not fulfil these requirements, but which for example easily crystallize, can optionally be of use in the course of synthesis and purification of the acid or of other salts. Suitable salts of the 2 - (4 - biphenylyloxy) - heptanoic acid produced according to the invention are in particular the alkali metal salts, such as the potassium, lithium and, particularly, sodium salt, also the alkaline earth metal salts and earth metal salts, such as the calcium, magnesium or aluminium salt, the ammonium salt, salts with primary, secondary or tertiary aliphatic or isocyclic bases and also secondary or tertiary heterocyclic bases, such as for example ethylamine, triethylamine, 2 - aminoethanol, 2,2′ - iminodiethanol, 2 - dimethyl - amino - ethanol, 2 - diethylamino - ethanol, ethylene diamine, benzyl amine, p - amino - benzoic acid diethylaminoethyl ester, pyrrolidine, piperidine, morpholine, 1 - ethyl piperidine, 2 - piperidino - ethanol, and also salts with basic ion-exchangers. The salts are produced in general by combining acid and base in suitable solvents, e.g. methanol, and optionally filtering off precipitated salts or evaporating the salt solutions. In place of free bases, corresponding, soluble carbonates, e.g. sodium or potassium carbonate or -bicarbonate can also be used. Moreover salts, which are relatively difficult to dissolve in the applied solvent, can also be produced by double reaction of another salt of the acid with a suitable salt of the base.

In a further aspect therefore, the present invention provides a pharmaceutical composition comprising 2 - (4 - biphenylyloxy) - heptanoic acid or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

The 2 - (4 - biphenylyloxy) - heptanoic acid and salts thereof are, as already mentioned, administered orally or rectally. Daily dosages vary between 50 and 500 mg for adult patients. Suitable dosage units, such as dragées (sugar coated tablets), tablets, sup-

positories preferably contain as active substance 10—250 mg, e.g. 50 or 100 mg of the acid or of a salt thereof with a pharmaceutically acceptable inorganic or organic base.

The content of active substance in dosage units for peroral administration is preferably between 10 and 90%. They are produced by combining the active substance with, e.g. solid pulverulent carriers, such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch of amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatin, optionally with the addition of lubricants, such as magnesium or calcium stearate or polyethylene glycols, to form tablets or dragée cores. These are coated for example with concentrated sugar solutions, which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to indicate the varying content of active substance. Other suitable dosage units for oral administration are hard gelatin capsules and also soft closed capsules made of gelatine and a softener such as glycerine. The former preferably contain the active substance as a granulate in admixture with lubricants such as talcum or magnesium stearate, and optionally stabilisers, such as sodium metabisulphite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as liquid polyethylene glycols, whereby likewise stabilisers can be added.

Applicable as dosage units for rectal administration are for example suppositories consisting of a combination of an active substance with a suppository base substance having a base of natural or synthetic triglycerides (e.g. cocoa butter), polyethylene glycols or suitable higher fatty alcohols, and gelatin rectal capsules, which contain a combination of the active substance with polyethylene glycols.

The following prescriptions explain in more detail the production of tablets and dragées:

a) 1000 g of 2 - (4 - biphenylyloxy) - heptanoic acid are mixed with 550 g of lactose and 292 g of potato starch. The mixture is moistened with an alcoholic solution of 8 g of gelatine and granulated through a sieve. After drying, 60 g of potato starch, 60 g of talcum and 10 g of magnesium stearate and 20 g of highly dispersed silicon dioxide are mixed in and from the mixture are pressed out 10,000 tablets each having a weight of 200 mg and a content of active substance of 100 mg. The tablets can if desired be provided with grooves for more accurate adjustment of the dosage.

b) 100 g of 2 - (4 - biphenylyloxy) - heptanoic acid are well mixed with 16 g of maize starch and 6 g of highly dispersed silicon dioxide. The mixture is moistened with a solution of 2 g of stearic acid, 6 g of ethyl cellulose and 6 g of stearine in ca. 70 ml of isopropyl alcohol and granulated through a sieve III (Ph.Helv.V.). The granulate is dried for ca. 14 hours and then put through a sieve III—IIIa. The granulate is then mixed with 16 g of maize starch, 16 g of talcum and 2 g of magnesium stearate and 1000 dragée cores are pressed out from the mixture. These are coated with a concentrated syrup of 2 g of shellac, 7.5 g of gum arabic, 0.15 g of dyestuff, 2 g of highly dispersed silicon dioxide, 25 g of talcum and 53.35 g of sugar and then dried. The obtained dragrées each weigh 260 mg and each contain 100 mg of active substance.

The following prescription further illustrates the production of suppositories:

A suppository composition is prepared from 10.0 g of 2 - (4 - biphenylyloxy) - heptanoic acid and 163.5 g of adeps solidus (solid fat) and 100 suppositories each having 100 mg of active ingredient are poured therefrom.

The following examples further illustrate the production of 2 - (4 - biphenylyloxy) - heptanoic acids and salts thereof but do not in any way restrict the scope of the invention. Temperatures are given in degrees centigrade.

Example 1

10 g (0.031 mol) of 2 - (4 - biphenylyl - oxy) - heptanoic acid ethyl ester are refluxed with 2.1 g (0.038 mol) of potassium hydroxide in 50 ml of methanol for one hour. The solution is then evaporated to obtain a syrupy consistency and mixed with water. If a clear solution is not obtained, the undissolved substance is removed by washing with ether. The alkaline solution is then acidified with 2N hydrochloric acid. The 2 - (4 - biphenylyl - oxy) - heptanoic acid first precipitates as an oil, which slowly crystallizes, particularly when rubbed with some methanol. It is purified by recrystallizing from methanol/water, from acetone/water or from hexane, B.P. 115—116°.

The ester required as the starting material is produced as follows:

a) In a round flask provided with stirrer, reflux condenser and drying tube containing potassium hydroxide, 3.68 g (0.16 mol) of sodium are dissolved in 150 ml of abs. ethanol. To the sodium ethylate solution thus prepared are added 27.2 g (0.16 mol) of pulverised p - phenylphenol and in the obtained solution of the sodium salt of the p - phenylphenol are then dissolved 35 g (0.1475 mol) of 2 - bromoheptanoic acid ethyl ester. The

obtained reaction solution is refluxed for 7 hours, whereby potassium bromide precipitates. The ethanol is evaporated off, the residue dissolved in ether and the solution shaken with 0.5N sodium hydroxide solution until an acidified sample of the alkaline extracts becomes nc longer cloudy. The ether solution is then shaken a further three times with 0.5N sodium hydroxide solution and thereafter with water. It is then dried over sodium sulphate and evaporated. The obtained 2 - (4 - bi - phenylyloxy) - heptanoic acid ethyl ester is chromatographically pure.

RF=0.9, silica gel neutral, benzene: ethanol=100:15.

EXAMPLE 2

29.84 g (0.1 mol) of 2 - (4 - biphenylyl - oxy) - heptanoic acid are dissolved in methanol. To the obtained solution are added 3.8 g (0.095 mol) of carbonate-free sodium hydroxide and the solution is evaporated until dry. The residue is separated from the starting material by extraction with ether, whereupon the pure sodium salt remains, which does not melt below 350°.

EXAMPLE 3

a) 1 g (0.00358 mol) of 2 - (4 - bi - phenylyloxy) - heptanoic acid nitrile is refluxed for 42 hours in a solution of 1 g of KOH in 35 ml of ethanol and 8 ml of water. (Besides the acid, only traces of the acid amide can afterwards be seen in a thin layer chromatogram). The reaction solution is acidified with 2N hydrochloric acid, the ethanol is evaporated in vacuo, the aqueous phase is extracted with ether and the ether is washed twice with water. After drying with $MgSO_4$, the ether phase yields the crude 2 - (4 - biphenyloxy) - heptanoic acid, which is recrystallised from a mixture of benzene/ligroin, m.p. 115—116°.

The 2 - (4 - biphenylyloxy) - heptanoic acid nitrile used as starting material is produced as follows:

b) In a round-bottomed flask which has been equipped with a stirrer, reflux condenser, dropping funnel and a drying tube containing potassium hydroxide, 57.0 g (0.5 mol) of ethyl cyano - acetate are dissolved in 200 ml of anhydrous ethanol. In order to prevent the temperature from rising above 60°, 11.5 g (0.3 mol) of metallic sodium are added in small portions to the solution. After about 2 hours, when the metallic sodium which has been added is completely dissolved, 75.5 g (0.5 mol) of n - pentyl bromide are added dropwise at a temperature of 40—50° and the resulting mixture is subsequently refluxed for 2 hours.

After cooling to room temperature, the reaction mixture is poured onto a mixture of ice and water, the oil which separates is taken up in ether and washed with water until a neutral reaction is obtained. The resulting ether solution is dried over sodium sulphate, filtered and then concentrated in a rotary evaporator. The residue is distilled in vacuo at an oil bath temperature of 140—150°. The ethyl 2 - n - pentyl - 2 - cyano - acetate boils at 117—119°/12 Torr.

c) To a flask which has been equipped with a stirrer reflux condenser and dropping funnel, 36.6 g (0.2 mol) of ethyl 2 - n - pentyl - 2 - cyano - acetate, 160 ml of water, 20.5 g (0.25 mol) of sodium acetate and a tip of a spatula of monoperphthalic acid are added and, while stirring well, 32 g (0.2 mol) of bromine are added dropwise at room temperature to this mixture. The reaction mixture is then heated for 2 1/2 hours at 60° and, after cooling, taken up in ether. The resulting ether solution is then consecutively washed with a dilute sodium bisulphite solution, a dilute sodium bicarbonate solution and then with water until a neutral reaction is obtained, dried over sodium sulphate, filtered and finally concentrated in a rotary evaporator. The residue is distilled in vacuo.

The ethyl 2 - n - pentyl - 2 - bromo - 2 - cyano - acetate obtained boils at 122—124°/10 Torr.

d) In a round-bottomed flask which has been equipped with a stirrer, dropping funnel and a drying tube containing potassium hydroxide 17.0 g (0.1 mol) of 4 - hydroxy - diphenyl are dissolved at room temperature in 350 ml of dimethyl formamide. 4.8 g (0.1 mol) of sodium hydride dispersion (50% dispersion in mineral oil) are then added with stirring. After completion of the conversion to the sodium salt, 26.2 g (0.1 mol) of ethyl 2 - n - pentyl - 2 - bromo - cyano - acetate are added dropwise at room temperature and the mixture is then heated for one hour while stirring on a water bath at a temperature of 60°. After cooling, the resulting reaction mixture is poured onto a mixture of ice and water. The oil which separates is extracted with ether and washed with 1N sodium hydroxide solution and water until a neutral reaction is obtained. The resulting ether solution is dried over sodum sulphate, filtered and then concentrated in vacuo. The residue is purified by column chromatography [silica gel (0.05—0.2 mm—Merck), using benzene as solvent]. After evaporation of the benzene and drying of the residue, the resulting ethyl 2 - (4 - biphenylyloxy) - 2 - n - pentyl - 2 - cyano - acetate crystallises, m.p. 56—59°.

e) In a round-bottomed flask equipped with a magnetic stirrer, 17.6 g (0.05 mol) of ethyl 2 - (5 - biphenylyloxy) - 2 - n - pentyl - 2 - cyano - acetate and 55 ml of 1N NaOH are stirred while heating for 2 hours at 80—90° (in place of aqueous 1N

NaOH, alcoholic 1N NaOH can also be used). After cooling, the reaction mixture which has been diluted with water is extracted with ether, the remaining aqueous phase is acidified with hydrochloric acid and the oil which separates is taken up in ether and then washed with water. The resulting 2 - (4 - biphenylyloxy) - 2 - n - pentyl - 2 - cyano - acetic acid is used as crude product in further processing.

f) 12.9 g (0.04 mol) of 2 - (4 - biphenyl - yloxy) - 2 - pentyl - 2 - cyano - acetic acid and a trace of metallic copper powder are mixed well and then cautiously heated over an open flame in a round-bottomed flask. At a temperature of 120° carbon dioxide begins to develop, whereby the temperature rapidly rises to 190°. To complete the decarboxylation, the temperature is raised for a short time (about 1 minute) to 200°. After cooling, the residue is recrystallised from ethyl alcohol in the presence of animal charcoal. The resulting 2 - (4 - biphenylyloxy) - heptanoic acid nitrile melts at 68—70°.

Example 4

a) 16 g (0.04 mol) of crude diethyl 4 - (biphenylyloxy - n - pentyl - malonate are refluxed in a solution of 5.4 g of KOH (85%) in 30 ml of methanol for 18 hours. After evaporating the methanol in vacuo, the residue is dissolved in about 500 ml of ice water and the resulting solution is acidified with 10 ml of concentrated hydrochloric acid. The colourless crystals which precipitate are washed with water and dissolved in 200 ml of methanol. After filtering, the 2 - (4 - bi - phenylyloxy) - heptanoic acid is precipitated by the dropwise addition of water, m.p. 114—115°. Diethyl (4 - diphenylyloxy) - n - pentyl - malonate is produced as follows:

b) While excluding carbon dioxide, 8.5 g (0.05 mol) of 4 - hydroxy - diphenyl are added to a solution of 1.15 g (0.05 mol) of sodium in 60 ml of anhydrous ethanol. 15.45 g of diethyl n - pentyl - bromo - malonate are added to the resulting solution and refluxed at the boil for 7 hours. The alcohol is then evaporated in vacuo, the residue is taken up in ether, and then shaken out three times with 0.5N sodium hydroxide solution and finally with water until a neutral reaction is obtained (pH=7).

After drying, concentration and chromatographic purification silica gel, eluant: benzene) a yellow, syrup-like oil is obtained, $n_D25=1.5334$.

Example 5

8 g of diethyl 4 - biphenylyloxy - n - pentyl - malonate are refluxed for 24 hours at the boil in a mixture of 20 ml of 5N sulphuric acid and 100 ml of glacial acid. After cooling the reaction mixture is poured onto 800 ml of ice water, whereby 2 - (4 - biphenylyloxy) - heptanoic acid separates as crystals. After recrystallisation from a mixture of benzene/ligroin, the purified acid melts at 114—115°.

Example 6

a) 1.5 g (0.00285 mol) of ethyl 2 - (4 - biphenylyloxy) - 2 - n - pentyl - 2 - cyano - acetate are refluxed for 24 hours at the boil in a solution of 0.8 g of KOH in 20 ml of ethanol and 2 ml of water. After evaporation of the ethanol in vacuo, the residue is acidified with 2N hydrochloric acid, extracted with ether, the ether phase is washed with water and dried over magnesium sulphate. After concentration, a mixture of 2 - (4 - biphenylyloxy) - 2 - carboxy - heptanoic acid amide, 2 - (4 - biphenylyloxy) - hep - tanoic acid and 2 - (4 - biphenylyloxy) - heptanoic acid amide is obtained. This mixture is refluxed for 20 minutes in xylene. After concentration, a mixture of 2 - (4 - biphenylyloxy) - heptanoic acid amide and the corresponding acid is obtained.

b) This mixture is refluxed for 40 hours in a solution of 1 g of KOH in 40 ml of ethanol and 5 ml of water and then further processed as described for the saponification of the nitrile (Example 3a). After recrystallisation from benzene/petroleum ether the resulting 2 - (4 - biphenylyloxy) - heptanoic acid melts at 115—116°.

c) The mixture of 2 - (4 - biphenylyloxy) - 2 - carboxy - heptanoic acid amide, 2 - (4 - biphenylyloxy) - heptanoic acid amide and 2 - 4 - biphenylyloxy) - heptanoic acid obtained in Example 6a) can also be saponified in acid medium:

0.6 g of the mixture obtained according to Example 6a) is heated in a mixture of 34 ml of 70% sulphuric acid (vol./vol.) and 17 ml of glacial acetic acid for 6 hours with stirring at a temperature of 90°. After evaporation of the acetic acid in vacuo, dilution with water and extraction with ether, and after drying of the ether, 2 - (4 - biphenylyloxy) - heptanoic acid is obtained. After recrystallising twice from benzene/ligroin the acid melts at 114—116°.

Example 7

8.5 g (0.05 mol) of 4 - hydroxy - di - phenyl are added to a solution of 2.3 g (0.1 mol) of sodium in 120 ml of anhydrous ethanol. After complete dissolution of the added substance, the solution is cooled to 0—5° and 10.45 g (0.05 mol) of 2 - bromo-heptanoic acid is added at the temperature. The reaction mixture is heated to the boil, the alcohol evaporated, the residue dissolved in water and the solution acidified with 2N hydrochloric acid. After recrystallisation from approximately 250 ml of 65% aqueous ethanol, the resulting 2 - (4 - biphenylyloxy)-

heptanoic acid (colourless crystals) melts at 113—115°.

EXAMPLE 8

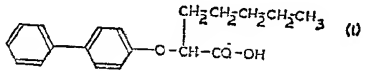
1 g (0.00335 mol) of 2 - (4 - biphenylyloxy) - heptanoic acid is dissolved in 20 ml of methanol and then added to a solution of 0.168 g (0.00254 mol) of KOH (86%) in 10 ml of methanol. The clear solution is evaporated to dryness and the residue is well washed with ether. The crystals are dissolved in hot ethyl acetate and filtered. After concentration of the filtrate, the crystalline potassium salt of 2 - (4 - biphenylyloxy) - heptanoic acid is obtained. The crystals decompose slowly above 300° without melting.

EXAMPLE 9

While excluding carbon dioxide, 0.4 g (0.01 mol) of calcium is decomposed in 40 ml of water. 6.5 g (0.0218 mol) of 2 - (4 - biphenylyloxy) - heptanoic acid in 150 ml of ethanol are added to the $Ca(OH)_2$ suspension and heated for 10 minutes at the boil. After concentration to dryness, the residue is triturated with ether and washed well. The resulting residue is extracted with hot methanol. Colourless crystals are obtained which slowly decompose above 290° without melting.

WHAT WE CLAIM IS:—

1. 2 - (4 - Biphenylyloxy) - heptanoic acid of the formula I



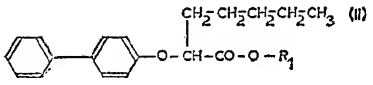
(I)

2. The pharmaceutically acceptable salts of 2 - (4 - biphenylyloxy) - heptanoic acid.

3. The calcium salt of 2 - (4 - biphenylyloxy) - heptanoic acid.

4. The sodium or potassium salt of 2 - (4 - biphenylyloxy) - heptanoic acid.

5. Process for the production of 2 - (4 - biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts which comprises hydrolysing an ester thereof having the general formula II



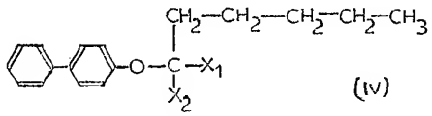
(II)

wherein R_1 represents a hydrocarbon radical and when required, converting a salt of 2-(4 - biphenylyloxy) - heptanoic acid thus obtained into the free acid or converting the 2 - (4 - biphenylyloxy) - heptanoic acid or a salt thereof thus obtained into, or into another, pharmaceutically acceptable salt thereof.

6. Process as defined in claim 5 wherein R_1 represents an alkyl group having maximally 6 carbon atoms, or a cyclohexyl, phenyl or benzyl group.

7. Process for the production of 2 - (4 - biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts which comprises hydrolysing the corresponding nitrile, or an amide or imidoalkyl ester thereof, any such imidoalkyl ester as aforesaid having at most 6 carbon atoms in the imidoalkyl ester moiety, and, when required, converting a salt of 2 - (4 - biphenylyloxy) - heptanoic acid thus obtained into the free acid or converting the 2 - (4 - biphenylyloxy) - heptanoic acid or a salt thereof thus obtained into, or into another, pharmaceutically acceptable salt thereof.

8. Process for the production of 2 - (4 - biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts, which comprises heating a (4 - biphenylyloxy) - n - pentyl - malonic acid derivative having the general formula IV



(IV)

wherein X_1 and X_2, independently of each other, represent a cyano group or an alkoxycarbonyl group having at most 7 carbon atoms, with an inorganic or organic base, until an equimolar amount of carbon dioxide is developed and, when required, converting a salt of 2 - (4 - biphenylyloxy) - heptanoic acid thus obtained into the free acid or into another, pharmaceutically acceptable, salt thereof.

9. Process for the production of 2 - (4 - biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts, which comprises heating (4 - biphenylyloxy - n - pentyl malonic acid or a salt thereof, until the equimolar amount of carbon dioxide is split off and, when required, converting a salt of 2 - (4 - biphenylyloxy) - heptanoic acid thus obtained into the free acid or converting the 2 - (4 - biphenylyloxy) - heptanoic acid or a salt thereof thus obtained into, or into another, pharmaceutically acceptable salt thereof.

10. Process for the production of 2 - (4 - biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts, which comprises reacting an alkali metal salt of p -

phenylphenol with a salt of a hydrohalic-, arenesulphonic- or alkanesulphonic-acid ester with respect to the 2 - hydroxy group of 2 - hydroxy heptanoic acid and, when required, converting a salt of 2 - (4 - biphenylyloxy) - heptanoic acid thus obtained into the free acid or into another, pharmaceutically acceptable, salt thereof.

11. 2 - (4 - Biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts whenever prepared by a process as claimed in any one of claims 5 to 7, 9 and 10.

12. 2 - (4 - Biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts whenever prepared by a process as claimed in claim 8.

13. Process as claimed in claim 5 substantially as hereinbefore described with reference to Example 1 or 2.

14. Process as claimed in any one of claims 7 to 10 substantailly as hereinbefore described with reference to any one of the Examples 3 to 9.

15. 2 - (4 - Biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts whenever prepared by a process as claimed in claim 13.

16. 2 - (4 - Biphenylyloxy) - heptanoic acid and its pharmaceutically acceptable salts whenever prepared by a process as claimed in claim 14.

17. A pharmaceutical composition comprising 2 - (4 - biphenylyloxy) - heptanoic acid, or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

18. A pharmaceutical composition as claimed in claim 17 substantially as hereinbefore described with reference to any of the foregoing prescriptions.

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